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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁶ : C07F 9/12, A61K 31/66, C07C 69/63, 69/017, 69/40, 69/42, 69/44, 39/26, 39/27, 39/28, A61K 31/225 | | A3 | (11) International Publication Number: WO 99/58555 (43) International Publication Date: 18 November 1999 (18.11.99) |
| (21) International Application Number: PCT/US99/10013 | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPo patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). | |
| (22) International Filing Date: 7 May 1999 (07.05.99) | | Published <i>With international search report.</i> | |
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| (74) Agents: STORELLA, John, R. et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111-3834 (US). | | | |
| (54) Title: WATER-SOLUBLE PRO-DRUGS OF 2,6-DIISOPROPYLPHENOL ANALOGUES | | | |
| (57) Abstract | | | |
| <p>This invention provides optionally substituted esters of propofol (2,6-diisopropylphenol). The propofol esters are soluble in water and metabolize rapidly to propofol in the body. The propofol esters are useful as pro-drugs for the same indications as propofol. This invention also provides methods of treating neurodegenerative diseases by administering an effective amount of propofol.</p> | | | |

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INTERNATIONAL SEARCH REPORT

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| International Application No PCT/US 99/10013 |
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A. CLASSIFICATION OF SUBJECT MATTER

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|----------------|-----------|-----------|------------|-----------|
| IPC 6 C07F9/12 | A61K31/66 | C07C69/63 | C07C69/017 | C07C69/40 |
| C07C69/42 | C07C69/44 | C07C39/26 | C07C39/27 | C07C39/28 |
| A61K31/225 | | | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07F A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | <p>TRAPANI G ET AL: "Propofol Analogs. Synthesis, Relationships between Structure and Affinity at GABAA Receptor in Rat Brain, and Differential Electrophysiological Profile at Recombinant Human GABAA Receptors" J. MED. CHEM. (JMCMAR, 00222623); 1998; VOL. 41 (11); PP. 1846-1854, - 28 April 1998 (1998-04-28) XP002112861 Universita degli Studi di Bari; Dipartimento Farmaco-Chimico Facolta di Farmacia; Bari; 70125; Italy (IT) GIVEN PUBLICATION DATE REFERS TO THE PUBLICATION ON INTERNET the whole document</p> <p>---</p> <p>-/-</p> | 1-61 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

23 August 1999

Date of mailing of the international search report

3. 12. 1999

Name and mailing address of the ISA

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BESLIER, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/10013

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | WO 93 21914 A (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 11 November 1993 (1993-11-11) the whole document --- | 1-61 |
| Y | US 5 529 989 A (GEORGE R. PETTIT) 25 June 1996 (1996-06-25) the whole document --- | 1-61 |
| Y | US 5 561 122 A (GEORGE R. PETTIT) 1 October 1996 (1996-10-01) the whole document --- | 1-61 |
| X | FR 2 555 608 A (TOYO JOZO KK) 31 May 1985 (1985-05-31) page 5, lines 25-26 and page 66, lines 5-6 --- | 1 |
| X | US 4 170 614 A (JOHN C. CRANO) 9 October 1979 (1979-10-09) the whole document --- | 1 |
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| X | KOSOLAPOFF G M ET AL: "Structural effects in reactions of organophosphorus compounds. I. Reactions of phosphorus oxychloride with hindered phenols" J. CHEM. SOC. C (JS00AX);1968; (7); PP.815-18, XP002112862 U. S. Air Force Acad.; Ff. J. Seiler Res. Lab. OAR; Colo. the whole document --- | 1 |

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INTERNATIONAL SEARCH REPORT

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| International Application No PCT/US 99/10013 |
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | <p>CHEMICAL ABSTRACTS, vol. 057, no. 3, 6 August 1962 (1962-08-06) Columbus, Ohio, US; column 3335i; XP002112866 abstract & K.C.JOSHI: "Organic pesticides VIII." J. INDIAN CHEM. SOC., vol. 39, no. 1, 1962, pages 5-8, ---</p> | 1 |
| P,Y | <p>TRAPANI G ET AL: "Water-soluble salts of amino acid esters of the anesthetic agent propofol" INT. J. PHARM. (IJPHDE,03785173);1998; VOL.175 (2); PP.195-204, XP002112863 Universita degli Studi di Bari;Facolta di Farmacia, Dipartimento Farmaco-Chimico; Bari; 70125; Italy (IT) the whole document -----</p> | 1-61 |

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US 99/10013**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 18-61 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

"see further info"

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-61

Pro-drugs of propofol corresponding to the formulas (1), (2) and (3), and pharmaceutical compositions containing them.

2. Claims: 62-66

Phenol derivatives of formula (19) and pharmaceutical compositions containing them.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/10013

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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